ZIEMAN

The Physiological Activities of Certain Derivatives of Diethyl Carbinamine

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THE PHYSIOLOGICAL ACTIVITIES OF CERTAIN DERIVATIVES OF DIETHYL CARBINAMINE

BY

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

William Walter Zieman

ENTITLED The Physiological Activities of Certain Derivatives of Diethyl Carbinamine

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

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THE PHYSIOLOGICAL ACTIVITIES OF CERTAIN DERIVATIVES OF DIETHYL CARBINAMINE

INTRODUCTION

For the production of general anaesthesia volatile bodies, which are rapidly absorbed and excreted, are most suitable. But these bodies do not fill their purpose when used to produce hypnosis for even if administered in small doses the resulting sleep rapidly passes away. Besides producing a sleep which has undesirable after effects, the manner of administering is inconvenient and for this reason less volatile liquid or solid substances, whose activity is only gradually set free in the organism, are being prepared.

In preparing such substances experimental work has shown that the presence of certain groups, radicles, or atoms has a pronounced effect in producing hypnosis. But before enumerating these it would be well to consider several points of a theoretical character as to the general processes which underlie the production of narcosis. Overton in his research work has shown that the velocity with which substances diffuse into the protoplasm varies. He divides these substances in order of their speed of diffusion; the first group containing univalent alchohols, aldehydes, petones, etc; the second, divalent alcohols and amides of mono - carboxylic acids; the third, glycerol, urea, etc., which are slightly diffusible; and fourth, salts of strong inorganic acids and bases which are completely impermiable.

The permiability increases in the homologous series and by the replacement of hydrogen by methyl or methyl by ethyl, etc.

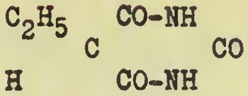
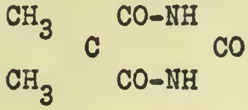
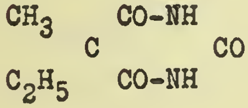
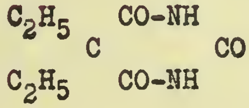
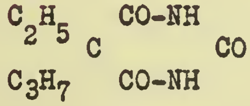
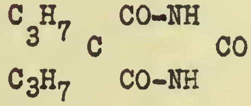
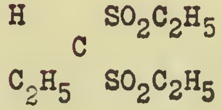
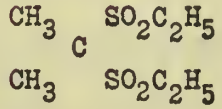
Now as a very general rule the rapidity of diffusion into membranes depends upon the solubility of substances in such bodies as fats, cholestrin, and lecithin, and Overton has brought forward the hypothesis that the magnitude of the distribution coefficient between fat and water determines the velocity of Osmosis. Both Overton and Hans Meyer draw attention to the fact, that as a rule, narcotics, anaesthetics, and antipyretics are substances which diffuse rapidly, and they consequently conclude that the narcotic value of a drug depends principally on its solubility in lipoid substances. Altho narcotics are all more or less soluble in water, there is no direct relationship between this solubility and narcotic power. Meyer tabulated the aliphatic narcotics according to the smallest molecular concentration which produced definite physiological effect, the values being expressed as fractions of the normal solution 1 g. molecule per liter, and termed "liminal values".

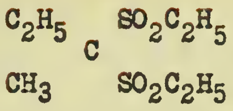
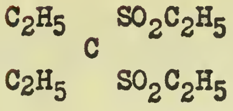
If these are compared with the "distribution coefficient", i.e. the ratio of the solubility in fats, S_F to their solubility in water S_W, it is found that the liminal values are smallest when the distribution coefficient is high - the most powerful narcotics are those which are most soluble in oil or fat and least soluble in water.(3)

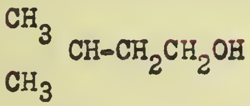
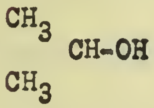
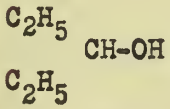
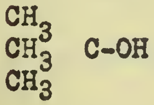
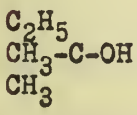
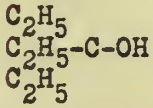
	Liminal Value	$\frac{S_F}{S_W}$ Distribution Coefficient
Trional	.0018	4.46
Tetronal	.0013	4.04
Sulphonal	.006	1.11
Chloral hydrate	.02	.22
Monacetin	.05	.06
Triacetin	.01	.3

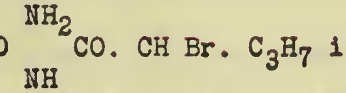
In preparing such substances experimental work has shown that the presence of such groups as the ethyl group has a pronounced effect in producing hypnosis. Both the bromine atom and propyl group have also been used to advantage but in the case of the latter prolonged after effects often resulted. The following table contains various compounds which show the effect of replacing

certain groups with ethyl and propyl groups. (4)

		Wt.of Animal lbs.	Dose Grams	Effect
Mono- ethyl- malonyl- Urea	 $\begin{array}{llll} C_2H_5 & & CO\text{-}NH & \\ & C & & CO \\ H & & CO\text{-}NH & \end{array}$	13	3-4	No effect
Dimethyl malonyl urea	 $\begin{array}{llll} CH_3 & & CO\text{-}NH & \\ & C & & CO \\ CH_3 & & CO\text{-}NH & \end{array}$	13	3	No effect
Methyl ethyl malonyl urea	 $\begin{array}{llll} CH_3 & & CO\text{-}NH & \\ & C & & CO \\ C_2H_5 & & CO\text{-}NH & \end{array}$	16.5	(1	No effect
			(3	Deep sleep after 1 hour lasting entire day
Diethyl malonyl urea	 $\begin{array}{llll} C_2H_5 & & CO\text{-}NH & \\ & C & & CO \\ C_2H_5 & & CO\text{-}NH & \end{array}$	16.5	1	Sleep after an hour.
			1.5	Sleep after 30 min. 24 hours duration.
Ethyl propyl malonyl urea	 $\begin{array}{llll} C_2H_5 & & CO\text{-}NH & \\ & C & & CO \\ C_3H_7 & & CO\text{-}NH & \end{array}$	17.5	1	Deep sleep after an hour lasting 24 hours
Diprophylmalonylurea	 $\begin{array}{llll} C_3H_7 & & CO\text{-}NH & \\ & C & & CO \\ C_3H_7 & & CO\text{-}NH & \end{array}$	16.5)) 17.5)	1	Deep sleep after 30 minutes for 48 hours, death-like sleep after 15 minutes, death next morning.
	 $\begin{array}{lll} H & & SO_2C_2H_5 \\ & C & \\ C_2H_5 & & SO_2C_2H_5 \end{array}$			Produces sleep and has toxic properties
Sulphonal	 $\begin{array}{lll} CH_3 & & SO_2C_2H_5 \\ & C & \\ CH_3 & & SO_2C_2H_5 \end{array}$			Produces sleep. In large doses produces condition resembling drunkenness

Trional	 $\begin{matrix} C_2H_5 & & SO_2C_2H_5 \\ & C & \\ CH_3 & & SO_2C_2H_5 \end{matrix}$	Has a more powerful and prolonged action than sulphonal.
Tetronal	 $\begin{matrix} C_2H_5 & & SO_2C_2H_5 \\ & C & \\ C_2H_5 & & SO_2C_2H_5 \end{matrix}$	Less soluble but the most powerful hypnotic of the above compounds.

Substance	Dose	Effect
CH_3OH	12 g	No action
C_2H_5OH	12	Sleep
C_3H_7OH	12	Sleep and death
 $\begin{matrix} CH_3 & \\ & CH\text{-}CH_2CH_2OH \\ CH_3 & \end{matrix}$	2	Half sleep
 $\begin{matrix} CH_3 & \\ & CH\text{-}OH \\ CH_3 & \end{matrix}$	2	Half sleep
 $\begin{matrix} C_2H_5 & \\ & CH\text{-}OH \\ C_2H_5 & \end{matrix}$	2	Sleep
 $\begin{matrix} CH_3 & \\ CH_3 & C\text{-}OH \\ CH_3 & \end{matrix}$	4	Sleep
 $\begin{matrix} C_2H_5 \\ CH_3\text{-}C\text{-}OH \\ CH_3 \end{matrix}$	2	Sleep
 $\begin{matrix} C_2H_5 \\ C_2H_5\text{-}C\text{-}OH \\ C_2H_5 \end{matrix}$	1	Sleep



Bromural $CO \begin{matrix} NH_2 \\ \\ NH \end{matrix} CO.\ CH\ Br.\ C_3H_7$ is said to be active owing to the isopropyl radical in valerianic acid, the activity being intensified by the presence of the urea grouping and the bromine atom.

Since the above results show that the presence of ethyl groups or a bromine atom has a decided effect in producing hypnosis, it is the purpose

in this thesis to prepare a base which shall contain ethyl groups and to combine with it acids which shall contain ethyl groups or ethyl groups and a bromine atom for the purpose of studying the physiological effects produced by the derivatives.

The base selected for the purpose was diethyl carbinamine which was first prepared by W. A. Noyes. (1) It was converted into the following derivatives: monosymmetrical secondary amyl urea, secondary amylamide of diethylacetic acid, and secondary amylamide of a bromo diethylacetic acid.

In the preparation of the amine the method of W. A. Noyes (2) was followed. It was obtained by distilling calcium propionate and converting the ketone thus obtained into the oxime which was then reduced to the amine. Several methods of reduction were tried; namely, aluminium amalgam, zinc dust and acetic acid, and sodium and absolute alcohol. Our purpose was to determine a quich method to take the place of the sodium absolute alcohol method which was long and required considerable absolute alcohol.

The first two methods, however, were unsatisfactory. The product obtained was very poor and the yield very low. The aluminium amalgam method gave the better results but since the yield was so low, the sodium reduction was always used and as much absolute alcohol recovered as possible.

Having thus determined the method for the preparation of the amine we can now take up its derivatives and their physiological effect on dogs.

The first, mono-symmetrical secondary amyl urea, was prepared by taking molecular proportions of diethyl carbin amine hydrochloride and potassium cyanate, the latter rearranging itself to form the urea.

The second, symmetrical secondary amyl amide of diethylacetic acid, was prepared by allowing two mols of the amine to react with one of diethylacetyl cholride, prepared by the malonicester synthesis.

The third, symmetrical secondary amylamide of a bromodiethyl acetic acid was prepared by allowing two mols of amine to react with one of a - bromo

diethyl acetyl chloride, the latter being prepared by the Hell-Volhard-Zelinsky method.

The α-bromo diethyl acetyl bromide was tried to be prepared by means of heating in a bomb in a water bath with bromine and diethyl acetyl chloride. This would have saved considerable time, for this bromide could be made to react directly with the amine. But the bomb exploded on heating and the entire contents were lost.

The physiological effects of the above compounds were determined by feeding the derivatives to dogs and are tabulated below.

Compound	Dose	Weight of Dog	Effect
Mono symmetrical secondary amyl urea	4 g.	30-40 lbs.	Produced drunkenness and drowsiness in 1 hour lasting 10 hours
Symmetrical secondary amyl amide of diethyl acetic acid	4 g.	30-35 lbs.	No action
Symmetrical secondary amyl amide of -bromo diethyl acetic acid	4 g.	30-40 lbs.	Vomited. Full stomach in 2½ hours. Empty stomach in 30 minutes.

EXPERIMENTAL

DIETHYL CARBINAMINE

Diethyl ketone was prepared by distilling calcium propionate which was made by dissolving 55 g. of calcium carbonate in 70 g. of propionic acid, diluted with 150 cc. of water. After the reaction was completed on warming, the mixture was evaporated to dryness on the steam bath and then distilled in round bottom Jena flasks. The ketone was obtained as a yellow liquid boiling at 101°C. (5)

The oxime of this ketone was prepared by placing in a glass stoppered bottle, one half of a mol (43 g.) ketone, 35 g. hydroxylamine hydrochloride, and 24 g. sodium hydroxide in 120 cc. of water. This mixture was shaken for one hour. The liquids were allowed to separate and the water layer was treated twice with ether and then dried with calcium chloride. The ether was distilled off and the remaining liquid added to the separated portion. The temperature was then raised to 150° C. which left almost pure oxime in the flask.

REDUCTION BY MEANS OF SODIUM AND ABSOLUTE ALCOHOL

This reduction was best carried out by taking the following proportions. Fifty grams of oxime, 900 cc. absolute alcohol, and 80 g. sodium. The oxime and about 125 cc. of alcohol were placed into a 2 liter round bottom flask connected to a reflux condenser. A piece of sodium, about 10 g., was then introduced which melted and floated around in the form of a globule. By the continuous addition of alcohol with each addition of sodium, the boiling point of the liquid could so be controlled that a molten globule of sodium would always float between the bottom of the flask and the layer of the liquid. The remaining

sodium was then added in about 5 g. portions followed by the addition of about 75 cc. of alcohol.

Since a large excess of alcohol was used, it was first removed by distilling the mixture of amine and alcohol on an oil bath until solid matter appeared in the flask. Into this distillate was passed dry hydrochloric acid until just faintly acid. This formed the hydrochloride of the amine from which the alcohol was obtained by distillation on an oil bath. Steam was then passed into the residue of the first distillation, which still contained some amine, and the distillate caught in dilute hydrochloric acid. This distillate and the residue from the alcohol distillation were then evaporated to dryness on a steam bath to obtain the hydrochloride. The yield of the amine hydrochloride from 124 g. of the oxime was 125 g.

REDUCTION BY MEANS OF ALUMINIUM AMALGAM

The amalgam was prepared by corroding grannular aluminium with a 10 percent sodium hydroxide solution and then washing three times with water. A 1 percent solution of mercuric chloride was then added to the water covered aluminium and allowed to work but a few seconds. The amalgam thus formed was again washed with water and finally with alcohol and ether. (6)

For the reduction 20 g. of the oxime in about 30 cc. of 50 percent alcohol and 16 g. of the amalgam were placed in a flask connected to a reflux condenser. Since no reaction took place in the cold the mixture was heated and a slight reaction took place. Heating was continued for several hours and the mixture then treated as in the sodium reduction except that no alcohol was recovered. The product was of a dark color and the yield very poor.

ZINC DUST AND ACETIC ACID

One hundred cc. of 1:1 acetic acid and 10 g. of oxime were placed in a 500 cc flask connected to a reflux condenser. Twenty g. of zinc dust were then slowly added and the solution warmed slightly. After the reaction appeared complete the mixture was filtered and the filtrate evaporated to dryness on a steam bath. The product in this case was also very poor and the yield very low.

SEPARATION OF THE FREE BASE

The separation of the free base from the hydrochloride was tried by three methods; treating with a strong solution of potassium hydroxide, extracting with ether, and distilling; mixing the hydrochloride with calcium hydroxide and distilling; and mixing the salt with lime and distilling.

For the first method 24 g. of the hydrochloride were dissolved in a little water and treated with about 50 to 75 cc. of 1:1 potassium hydroxide. The amine was separated and distilled. It contained a little water. When the potash solution was extracted with ether a bad emulsion was formed from which it was difficult to separate the two liquids. When the ether solution was distilled to remove ether, the amine distilled over with it as the temperature rose. In other words the amine could not be separated by fractional distillation from the ether-amine solution.

In the second method 24 g. of the hydrochloride were mixed with 50 g. of calcium hydroxide and distilled from a retort. The amine in this case contained considerable water due to the reaction of the hydrochloric acid with the hydroxide.

In the third method 24 g. of the hydrochloride were finely ground and mixed with 50 g. to 60 g. of finely ground lime prepared from marble. This mixture was placed in a retort and distilled over a free flame. In this case the

water set free during the reaction combined with the lime and formed calcium hydroxide. The liquid obtained was colorless and hardly reacted with sodium. The yield was 18 g.

$$\mathrm{Ca\ O} \quad 2 \quad \mathrm{Amine.\ HCl} \qquad \mathrm{Ca\ Cl_2} \qquad \mathrm{H_2O}$$

$$\mathrm{Ca\ O} \quad \mathrm{H_2O} \qquad\qquad \mathrm{Ca\ (OH)_2}$$

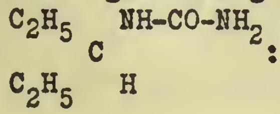
This method was used for the remaining work.

SECONDARY

SYMMETRICAL AMYL UREA

Twenty g. cf diethyl-carbin amine hydrochloride were weighed out and dissolved in about 40 cc of water. A solution of 13 g. cf potassium cyanate in about 30 cc of water was then added and the mixture allowed to stand for five days. A network of crystals formed from which the liquid was decanted. The crystals were washed several times with water and then dried.

The urea crystallizes from dilute alcohol in the form of small white needle-shaped crystals which are very soluble in alcohol. It is slightly soluble in cold water but more soluble in hot. The meeting point, corrected, is 188-189° C. 0.2083 g. subs. gave 40.15 cc. N_2; (21° and 746 mm. over KOH)

Calc. for 

$$\begin{matrix} C_2H_5 & & NH\text{-}CO\text{-}NH_2 \\ & C & \\ C_2H_5 & & H \end{matrix}$$

: N,21.54; found 21.66 percent.

SYMMETRICAL SECONDARY AMYL AMIDE OF DIETHYL ACETIC ACID

The synthesis of this compound involved the preparation of diethyl acetyl cholride which was prepared from diethyl acetic acid.

To a 2-liter flask connected to a reflux condenser was added 300 cc. of absolute alcohol and 23.1 g. cf sodium in small portions. The mixture was cooled and 160 g. cf malonic ester were added. After shaking, the mixture was warmed to about 50° C and 150 cc of ethyl bromide added in four equal proportions.

After each addition the mixture was cooled. When all of the ethyl bromide had been added, the flask was placed on a water bath and the contents were heated until no longer alkaline. The alcohol was distilled off over a salt water bath. About a liter of water was then added and the monoethyl malonic ester extracted three times with ether. The ether solution was dried with calcium chloride and distilled. The portion boiling from 200-215° C was taken as fairly pure. Yield 149 grams.

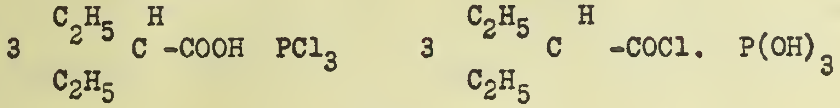
Diethyl malonic ester was prepared by adding to a flask connected to a reflux condenser 250 cc. of absolute alcohol and 18.4 g. of sodium in small portions. This mixture was cooled and the mono ethyl ester added. The mixture was heated up to about 50° C after shaking and 150 g. of ethyl iodide were added in four equal portions, the contents being cooled after each addition. The mixture was then heated over a salt water bath until the contents reacted no longer alkaline. The alcohol was distilled off over a salt water bath and the remaining liquid treated with about a liter of water and extracted three times with ether. The ether solution of the diethyl malonic ester was dried with calcium chloride, and the ether distilled off. The portion boiling from 212-225° C was taken as pure ester. Yield 132 g.

The diethyl malonic ester was then saponified by adding slowly 101 grams of potassium hydroxide in 101 cc. of water to the boiling ester in 68 cc. of alcohol. Boiling was continued for 30 minutes and the mixture was then evaporated to dryness on the water bath. About 140 grams of ice were then added to the dried mass and upon it were poured 155 cc. of conc. hydrochloric acid. The mixture was extracted three times with ether and dried over sodium sulphate for three days. The ether was distilled over on a water bath and the last traces were removed in a vacuum dessicator over sulphuric acid. This left a white crystalline mass which was further dried on a porous plate. Yield 35 grams.

The diethyl acetic acid was prepared by treating the diethyl malonic acid in a flask placed in an oil bath to about 175° C until carbon dioxide ceased

to come off. This required about one hour. The liquid was then distilled and the fraction boiling from 182-190° C taken. Yield 53.5 grams.

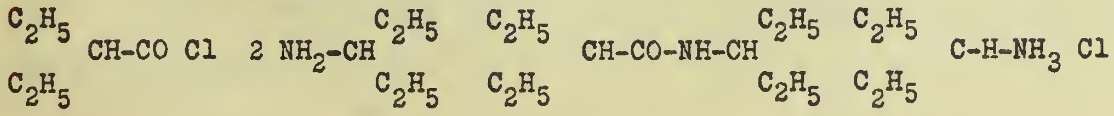
Diethyl acetyl chloride was prepared by placing 34.8 grams of diethyl acetic acid in a 200 cc.(7)



$$3\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\overset{H}{C}\text{ -COOH}\quad PCl_3\qquad 3\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\overset{H}{C}\text{ -COCl.}\quad P(OH)_3$$

distilling bulb and adding to it 17.2 g. of phosphorus trichloride. The stem of the distilling flask was bent up at an angle of 60° and connected to a condenser, in the end of which was fastened a bent glass tube which dipped into 10 cm. of conc. sulphuric acid. Thus the contents of flask were kept under pressure of 10 cm. of conc. acid. This minimized the secondary reactions when temperature was kept at 18° C. After standing 6 hours contents were heated in a water bath for about 30 minutes. The acid chloride was then poured off from the syrupy phosphoric acid and distilled. The fraction boiling at 130-140 C was taken. Yield, 35 grams.

The amide was prepared by allowing 2 parts of the amine to react with 1 of the acid chloride. For the preparation 46 g. of the amine were placed in a two liter flask connected to a reflux condenser. Thirty-five g. of the acid chloride mixed with about 500 cc. of anhydrous ether were then slowly added thru the top of the condenser. The reaction was very vigorous and the flask was placed in ice water and continually shaken. After all of the acid chloride was added the ether was filtered off and the filter washed two or three times with ether. The amide is fairly soluble in ether but considerable remained behind mixed with the hydrochloride of the amine which was formed by the reaction as shown by the equation



$$\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\text{CH-CO Cl}\quad 2\,NH_2\text{-CH}\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\quad\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\text{CH-CO-NH-CH}\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\quad\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\text{C-H-}NH_3\text{ Cl}$$

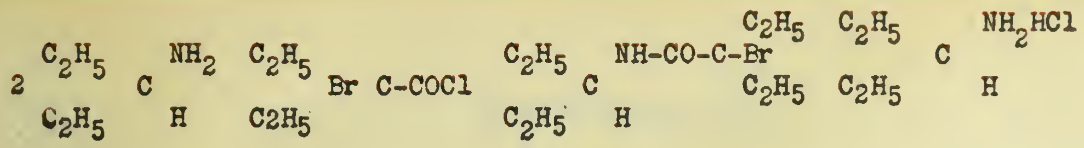
This was treated with boiling water which dissolved the hydrochloride. The amide was filtered off, washed, and added to the first portion from which the ether was evaporated. The amide was then recrystallized from dilute alcohol. Yield, 31 g. It is a white, very light crystalline substance, difficultly soluble in both hot and cold water. It is readily soluble in ether and very soluble in alcohol. It melts at 205.5-206° C. (Corrected)

	Determined	Calculated
Nitrogen	7.55%	7.51%

SYMMETRICAL SECONDARY AMYL AMIDE OF BROMO DIETHYL ACETIC ACID

This involved the preparation of bromo diethyl acetic chloride which was prepared by brominating diethyl acetyl chloride. (8)

The same apparatus was used here as in the preparation of the acid chloride with one exception. The tube leading from the end of the condenser did not dip into any liquid but led into a flask of NaOH about an inch above liquid layer. This absorbed the HBr_2 which was liberated. Twenty-six g. of the acid chloride were poured into the flask and heated on a water bath. Thirty-two g. of bromine were then slowly allowed to drop in. Care was taken to regulate the flow so as not to have any bromine distill over. After all of the bromine was added the excess was boiled off and the remaining liquid subjected to vacuum distillation. The manometer registered 17 mm. and the liquid started to come over at 70° C. It came over slowly until 85° C was reached at which point another fraction 85-93° was taken. This fraction contained mostly the bromo acid chloride. The boiling point according to Beilstein was 90-110° at 20 mm. Yield, 39 grams.



$$2\;\begin{matrix}C_2H_5\\C_2H_5\end{matrix}C\begin{matrix}NH_2\\H\end{matrix}\quad\begin{matrix}C_2H_5\\C2H_5\end{matrix}Br\;C\text{-}COCl\quad\begin{matrix}C_2H_5\\C_2H_5\end{matrix}C\begin{matrix}NH\text{-}CO\text{-}\overset{C_2H_5}{\underset{C_2H_5}{C}}\text{-}Br\\H\end{matrix}\quad\begin{matrix}C_2H_5\\C_2H_5\end{matrix}C\begin{matrix}NH_2HCl\\H\end{matrix}$$

The method of preparing the brom-amide was exactly the same as for the other amide. Thirty-five g. of diethyl carbin amine and 39 grams of bromo acetyl chloride were used. The brom amide was however more soluble in ether and was found to be all in the ether solution. The ether was evaporated off and the crystals pressed on a porous plate. The amide was purified by recrystallizing from dilute alcohol. The melting point was below 100° C and on cooling, mixture was vigorously shaken so as to form small crystals. They had a slight yellow tinge and melted at 53° C. The amide was slightly soluble in water but readily soluble in alcohol and ether.

	Determined	Calculated
Nitrogen	5.53	5.31

PHYSIOLOGICAL TESTS

The dog was a female, fox terrier, weighing between 30 and 40 lbs. One gram of urea was weighed out and mixed with a small amount of ground meat and fed to the dog. The animal was given several pieces of fresh meat and then the portions mixed with the urea. Since no effects were apparent the dose was doubled the following day. This also had no effect and the next day 4 g. were given. This had no effect within 30 minutes but in an hour made her drowsy and intoxicated. The dog would get up and stagger and then fall down heavily and sleep lightly. She was in this condition for about 10 hours.

The amide was tried on a black male weighing about 30 to 40 lbs. He looked like a fox terrier but his nose was too blunt. He was given a one-gram portion mixed with ground raw meat but since it had a sharp taste he spit it out. He was then given it in a capsule which was surrounded with raw meat. No effects could be noticed. The next day he was given two grams in capsules in the same manner, and again no effects could be noticed. He was then given four grams but would not take them. They were then thrown in his mouth and washed down with water. It had no effect on him whatever.

The brom amide was tried on a large black dog weighing about 40 pounds. One gram was weighed out and placed in a capsule which was surrounded with raw meat and fed to the dog. This had no effect and the following day he was given two grams in the same manner which likewise had no effect. He was then given four grams and at the end of two and one-half hours vomited. He had previously been fed when this was given. After resting a day he was again given four grams which caused him to vomit within thirty minutes.

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